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Evidence and decision-making in times of pandemic

Evidencias y decisiones en tiempos de pandemia

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In December 2019, an outbreak of a respiratory desease caused by a new coronavirus strain was detected in Wuhan, China. The disease spread rapidly around the world and was recognized as a pandemic by the World Health Organization in March 2020.

From the very beginning of the pandemic, society was faced with a scenario fraught with uncertainty: a new disease with severe effects on some patients and no specific treatment. The medical community reacted promptly and undertook the quest for treatment options, some based on prior experiences with diseases caused by other coronavirus strains or related viruses, and other approaches based on potential pathophysiological mechanisms - promising at the time - but without any supporting scientific evidence.

Thus, medications like hydroxychloroquine took center stage, bolstered by the opinions of "renowned" scientists (1,2), but supported by poor-quality studies. Hope and haste showcased it as an effective therapy - despite many unanswered questions - unleashing demand for a medication of doubtful effectiveness and safety (3,4). The situation with hydroxychloroquine and other medications became even more convoluted when well-known government leaders and politicians in Colombia and other parts of the world made statements regarding potential curative treatments for COVID-19 (chloroquine, ivermectin and fresh frozen plasma were the most frequently mentioned), triggering shortages and offering false hopes to their followers and supporters.

Showing that a treatment is really effective requires an impartial and unbiased assessment by means of a study known as a clinical trial, in which an experimental treatment is given to a group of randomly assigned patients and compared against the standard or control treatment, frequently against placebo. Ideally, this process must be blinded so that the researchers have no way of knowing what intervention the patients received, drug or placebo, and must have a follow-up period during which good and bad outcomes are assessed. Such a design allows to control for biases and to determine, with the greatest possible certainty, whether a medication is actually better or more efficacious than the control.

In order to avoid bias, clinical trials must meet the highest scientific standards. All treatments must be studied in clinical trials, regardless of their origin or their classification as conventional, complementary or alternative. Unverified theories, information based on personal experiences, years of experience using a treatment, reputation, optimism or wishful thinking are not enough to ensure the effectiveness and safety of any treatment. Without this painstaking process, useless or even harmful treatments might end up being prescribed merely on the grounds that they are "thought or believed" to work (5). Needless to say, these studies are not the sole source of causality evidence and they are subject to bias, as is the case with other forms of scientific evidence (6).

It is our duty to demand that all available health care recommendations be based on sound scientific data, even if this is not always possible. Uncertainty in scientific thinking is inevitable, and providing completely sound recommendations in times of crisis is simply unfeasible (7). During a pandemic, a large proportion of the information is sketchy and comes from many different sources; it may elicit various interpretations, and striking a balance between acting on the basis of what is available or being cautious,

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is a very difficult decision to make (8). In difficult times, it is even more important to abide by the principles of evidence based medicine as a strategy to improve the odds of obtaining the right answers to countless questions (9).

In critically ill patients with SARS-CoV-2 infection, the development of acute respiratory distress syndrome occurs very quickly and is associated with high mortality. Given the unavailability of specific effective therapies, the recommendation is to implement supportive measures, that is to say, everything that is available in terms of intensive care developments, knowledge and technology. In view of a scenario where there is no specific treatment for a very severe disease, the feeling of "failing to do anything to avoid death" has led to the "compassionate" use of treatments. In other words, acting out of despair to provide treatments that are not recommended or authorized and which could also be potentially dangerous besides being inadequate.

Any such intervention creates a false sense of reassurance, which is quite a serious problem. Tied to the use of those medications is the mistaken assumption that the probability of a beneficial effect is higher than the probability of causing harm, something which is far from real, considering the absence of clinical trials to support it (10). For example, if the patient dies after receiving the medication, the assumption is that the disease was the cause of death: "It was a very severe disease and the medication could not do much for the patient." If, on the other hand, the patient survives, the outcome will be attributed to the new medication. In fact, the cause of death may have been directly or indirectly associated with the medication in a patient who could have even had a chance of surviving on supportive treatment. Consequently, the assumption (disease-related death vs. drug-related survival) is flawed. As explained previously, it is impossible to determine whether a drug is useful or not without a control group of patients that have not received the intervention, i.e., without verification by means of a clinical trial (in epidemiology, this scenario is referred to as counterfactual). If a drug has not gone through this type of study to demonstrate safety and efficacy, it is reckless and potentially dangerous to recommended it for the treatment of any disease.

Moreover, compassionate use is fueled by the notion that no evidence will become available in the course of months, or even years. However, this is not true in the case of COVID-19, given that more than 1500 clinical trials are currently under way and registered in www.clinicaltrials.gov, the most important database for the registration of these studies in the world. In other words, within weeks or months, more than 1500 studies will begin to provide results on the effectiveness and safety of several interventions. That means that evidence will soon be available on what works and what does not. The challenge - as evidence begins to emerge - lies in the ability to analyze, filter and interpret the information in order to gain insight into what is useful, how uncertain results are, and their applicability in different settings.

This is where systematic reviews of the literature play a critical role. For example, a physician who comes across a clinical trial that shows that drug A results in a slightly shorter length of stay and reaches a conclusion based only on that study, could assume that the result is an irrefutable truth. Only high-quality literature reviews and, more recently, living systematic reviews, allow to summarize and synthesize all the available clinical trials, assess their quality, conduct a critical analysis and arrive at the most accurate conclusions possible for issuing treatment recommendations. Creating a detailed, clear and highly meaningful recommendation requires a complex, rigorous and systematic process to ensure its quality.

At the start of the pandemic, panic took over; overwhelmed by lack of evidence and despair many felt compelled to use medications with no support from the evidence. However, time has gone by and evidence has begun to emerge and will continue to do so for months to come. We are now in a second stage of transition where we have learned about the virus and its mechanisms. Nonetheless, we need to be clear: there is no medication which, to this date, has been shown to be effective and safe in preventing contagion, treating mild forms or reducing complications.

Perhaps the sole exception so far is the use of steroids (dexamethasone) which, in critically ill patients, has been shown to reduce days on mechanical ventilation, and possibly mortality as well (11). It is important to highlight that its use is restricted to hospitalized patients under specific conditions; and several ongoing trials will help support, confirm or rule out this effect. Medications such as remdesivir have shown only a small effect over time until symptom resolution and require further research (12). To date, other drugs such as ivermectin, chloroquine, interferon, azithromycin, lopinavir/ritonavir, tocilizumab, or interventions such as convalescent plasma, lack consistent evidence supporting their use at any stage of the disease. Besides increasing healthcare costs, their use may expose patients to unnecessary risks.

We will soon enter a third phase, when the evidence of this huge number of ongoing studies will become available. By then, we might have been able to identify a treatment or ruled out the effectiveness of many. We still hope for a vaccine to prevent the disease, with sufficient scientific underpinning for large-scale use. Time will tell.

In short, determining the effectiveness and safety of a pharmacological treatment is no easy task, as it requires rigorous research mainly in the form of clinical trials. Moreover, when results are available, they need to be identified, assessed and summarized in order to arrive at valid and accurate conclusions by means of systematic reviews of the literature. It is only after evidence is summarized that credible and rigorous recommendations can be provided regarding the best and

safest treatments, following an explicit methodology. Then, and only then, will we be able to avoid the risk of creating false hopes, increasing healthcare costs unnecessarily or, what is even worse, recommending medications that could result in harm or even death.

These are difficult times, but our appeal is that we all act with caution, particularly as pertains to pharmacological interventions. Lack of evidence regarding the effectiveness of certain medications cannot be the rationale for the indiscriminate use of interventions of unknown effects. Given the great number of ongoing studies, we will slowly gain access to more, and hopefully better, evidence to offer safer and more adequate treatments. We are now at the point where, for the good of our patients and of the health systems, no decision should be made without a critical analysis of the literature. The words of Hippocrates are more relevant today than ever before:"primum non nocere".

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